UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,696	03/25/2004	Gudmundur Johannsson	31611-5A	6059

24256 7590 10/05/2004

DINSMORE & SHOHL, LLP
1900 CHEMED CENTER
255 EAST FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/808,696	JOHANNSSON ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT OF PRELIMINARY AMENDMENT, IDS AND STATUS OF THE CLAIMS

1. The preliminary amendment and information disclosure statement (IDS) and Form PTO-1449 filed 3/25/04 are acknowledged, entered and considered. In view of Applicant's request claims 1-10 have been canceled and claims 11-18 have been added. Claims 11-18 are now pending in the application. With respect to the IDS and Form PTO-1449, the references cited therewith on Form PTO-1449 are not provided in the instant application. However, as *per* Applicant's request, since the cited references were considered previously in the parent application Serial No. 09/050,366; pursuant to CFR § 1.98(d), the references cited in Form PTO-1449 in this application have been considered and signed as requested by Applicant.

TITLE OF INVENTION IS NOT DESCRIPTIVE

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: A method for treating a patient having metabolic syndrome.

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH.

3. Claims 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a patient having Metabolic

Syndrome comprising Primary Insulin Resistance and exhibiting lipoprotein aberration or hypertension, wherein said method comprises administering to said patient recombinant human growth hormone (rhGH) in an amount effective for decreasing lipoprotein aberration or hypertension of said patient, does not reasonably provide enablement for treatment of a method comprising administering to said patient all kinds of growth hormones or functional analog thereof as claimed in independent claim 11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with independent claim 11.

The specification does not adequately teach the treatment and use of all kinds of growth hormones wherein the growth hormone comprises human growth hormone or a functional analog thereof or the growth hormone comprises human growth hormone as claimed in claims 11, 12 and 14-18; rather, the specification teaches the use and/or administration of rhGH for treating a patient having Metabolic Syndrome to decrease insulin resistance or lipoprotein aberration or hypertension as disclosed in Figures 1-3 and Tables 1-4 in the instant specification. Figures 1-3 and Tables 1-4 show that 9 months of rhGH treatment in middle-aged men with abdominal/visceral obesity reduced total body fat, total cholesterol, triglycerides and diastolic blood pressure and resulted in specific and marked decrease of both abdominal, subcutaneous and visceral adipose tissue in comparison with placebo groups by the various assays disclosed in the Tables and Figures. However, the use of growth hormones in general for treatment purposes as claimed are not justified by the mere recitation/definition on page 3, lines 17-20 in the

instant specification which states that the present invention thus relates to the use of growth hormone or analogues thereof as claimed the claims file (e.g., claim 11). By analog is meant a substance having the same biological activity as described here and having at least 65% homology with natural occurring growth hormone (i.e., which may encompass or include growth hormones from various species, such as bovine, porcine, equine, ovine, rodent, etc.). Thus, Applicant has not shown that the various growth hormones defined in the specification and claimed would be effective as the exemplified rhGH formulations for the following reasons:

Applicant acknowledges in the instant specification on page 2, lines 14-19 that in spite of the replacement therapy with rhGH which demonstrated favorable effects on most of the features of GH deficiency in adults; however, there has never been investigation whether rhGH treatment can improve the metabolic abnormalities observed in abdominal/visceral obesity, except the instant invention uses randomized, double-blind, placebo-controlled design to evaluate the effects of rhGH administration in patients with abdominal/visceral obesity. Further, with respect to the dosage ranges, the instant specification on page 5, lines 5-12 states that the daily rhGH dose was 9.5 μg/kg (0.20 IU/kg body weight/week) administered subcutaneously and the dose was reduced by half in the event of side effects. Thus, showing clearly the unpredictability of the dosage regimen even in the exemplified rhGH, let alone using all kinds of growth hormones for the claimed treatment.

Furthermore, the reference of Holly et al (J. Endocr., Volume 118, pp. 353-364, 1988) reviews the role of growth hormone in diabetic patients. The reference on page

357, right column shows the unpredictability of GH molecule in diabetic patient (i.e., is the GH molecule itself different in diabetes?) because circulating GH is a heterogenous family of closely related peptides as examined by several investigators. Although, a number of GH molecule variants have been described, only two have been found in circulation in appreciable amount in man, these being the normal 22,000 Dalton (22 kDa) GH and a 20 kDa GH form differing from the former by a 15 amino acid deletion produced by alternative splicing of GH mRNA. In addition, it is well recognized that circulating GH elutes from gel filtration columns in three size forms with molecular weights of approximately 22 kDa, 45 kDa and 80-90 kDa (known classically as GH, big-GH and big-big-GH, respectively). Thus, the GH molecule can vary with the nature of the protein, its source, and its binding conditions resulting in differences of immunological properties. Moreover, the reference of Salomon et al (N. Engl. J. Med., Vol. 321, No. 26, pp. 1797-1803, Dec. 28, 1989) teaches the effects of treatment with rhGH on body composition and metabolism in adults with growth hormone deficiency, wherein treatment with rhGH increased the mean lean body mass, and decreased the fat mass; while in the group treated with growth hormone, neither changes significantly in the placebo group. Further, the basal metabolic rate, measured at base line and after one and six months of rhGH administration, increased significantly. Also, fasting plasma cholesterol levels were lower in the rhGH-treated group than the placebo group, whereas plasma triglyceride values were similar in the two groups throughout the study. Hence, in adults with growth hormone deficiency, six months of treatment with rhGH

had a marked effect on body composition, resulting in an increase in lean body mass and a decrease in fat mass (See e.g., abstract, Figures, Tables and pages 1801-1802).

Thus, clearly demonstrating favorable effects of rhGH on the multiple perturbations associated with abdominal/visceral obesity, or for decreasing lipoprotein aberration or hypertension and as such, Applicant has not shown that the various growth hormones disclosed would be used in the manner claimed; except for the rhGH exemplified.

Therefore, in view of the above, the scope of treatment of a method comprising administering to said patient all kinds of growth hormones or functional analog thereof as claimed in independent claim 11 would involve tests for various growth hormones in all kinds of situations (i.e., there is no adequate disclosure in the instant specification to show the broad spectrum of administering growth hormone or a functional analog thereof claimed intended for a method of treating a patient having Metabolic Syndrome comprising Primary Insulin Resistance and exhibiting lipoprotein aberration or hypertension, wherein said method comprises administering to said patient hGH or a functional analog thereof in an amount effective for decreasing lipoprotein aberrations or hypertension of said patient as claimed in claim 11). It would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since administration of numerous growth hormones or functional analog thereof are contemplated and are encompassed as well as wide range of situations. The results

desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Thus, one of ordinary skill in the art would not be able to show that all treatment conditions as well as administration of all kinds of growth hormones or functional analog thereof are encompassed in the claims would be used as claimed in independent claim 11 in the instant invention. Thus, Applicant has not established any *nexus* between the various claimed growth hormones or functional analog thereof and their use in the manner claimed in claim 11.

Further, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicant is not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for all kinds of growth hormones or functional analog thereof as well as method of treatment using the various growth hormones claimed thereof. Thus, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims for the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data and the breadth of the claims; the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 11-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 12 are indefinite in the recitation "functional analog thereof". Although, on page 3, lines 19-20 in the instant specification "analog" is defined as a substance having the same biological activity as described here and having at least

65% homology with natural growth hormone; however, it is not clear or defined what is meant by "a functional analog thereof", and as such render the claims indefinite as to the claims metes and bounds.

Claim 12 is indefinite in depending upon canceled claim 1. Appropriate correction is required.

CLAIM REJECTIONS-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansson et al (Metabolism, Vol. 44, No. 9, pp. 1126-1129, September 1995) taken with Rosen et al (Acta Endocrinologia, Vol. 129, pp. 195-200, 1993) and Reaven et al (N. eng. J. Med., Vol. 334, No. 6, pp. 374-381,1996).

The primary reference of Johansson et al teaches that Growth Hormone-Deficient Adults Are Insulin-Resistant (See e.g., Abstract including the Title). Under Discussion, on page 1127, the reference states that the present study indicates that growth hormone deficient (GHD) patients are insulin resistant. Glucose insulin rates (GIRs) were less than half those of controls, both when calculated according to body weight and when corrected for body fat. The results show a decreased sensitivity to insulin in peripheral tissue in adults with GHD. On page 1128, left column, paragraph 3, the reference states that serum triglyceride levels are higher in adults with GHD, with a tendency also in the present GHD patients. On the same page right column, paragraph 2, continues by stating that hyperinsulinemia is a common feature in all other states involving insulin resistance, such as obesity, hypertension, and non-insulin dependent diabetes mellitus. Further, the reference Johansson et al. on page 1128, right column bridging page 1129 states that in a previous study, we showed that rhGH treatment induced a markedly worsened insulin resistance after 6 weeks, due to a decrease in the effect of insulin on glucose utilization. However, after 6 months of rhGH treatment, insulin sensitivity was restored to baseline values. Hence, showing a transient phenomenon wherein insulin sensitivity can deteriorate during rhGH treatment. Furthermore, the reference suggests that hypothetically, a further improvement in

insulin sensitivity is possible, since exercise capacity and physical activity continue to improve beyond the first 6 months of rhGH treatment. Thus, the reference teaches the use of growth hormones to decrease insulin resistance associated with metabolic syndrome, which may include lipoprotein aberration or hypertension. Therefore, the primary reference clearly teaches as disclosed on page 1129 that the use of growth hormone would result in favorable changes in body compositions, such as an increase in lean body mass and a decrease in abdominal and visceral adipose tissue which is induced by rhGH treatment the insulin antagonist effect of GH.

The primary reference of Johansson et al differs from claims 11-18 in not teaching the use of growth hormone fro decreasing lipoprotein aberration or hypertension in a patient. However, Rosen et al show that growth hormone deficiency alters lipoprotein metabolism and increases the risk for development of hypertension, which in turn might contribute to the increased risk of cardiovascular disease as well as insulin resistance which result in diabetic patients (See e.g., Abstract, Table 3 and page 199). On page 200, the reference concludes by stating that growth hormone is important for the regulation of lipoprotein metabolism during adult life. Lack of GH results in higher triglyceride concentrations and lower HDL concentrations, changes that may contribute to increased risk of cardiovascular death in GH deficiency and suggests replacement therapy with GH to adults with GH deficiency. Thus, motivating one of ordinary skill in the art to administer an effective amount of GH for the intended purposes of decreasing lipoprotein aberrations or hypertension in a patient.

Further, the review article of Reaven et al shows the changes in glucose, insulin, and lipoprotein metabolism in patients with hypertension, and examines the role of the sympathoadrenal system in the development of hypertension and the related metabolic changes because abnormalities of glucose, insulin, and lipoprotein metabolism are common in patients with hypertension (See e.g. page 374). Figure 3 discloses the hypothetical relation between insulin and blood pressure in patients with obesity-related hypertension, and Figure 5 shows the postulated relations among insulin resistance, high blood pressure, and increased cardiovascular risk. On page 380, the reference concludes by stating, according to this hypothesis (i.e., Figure 5), insulin resistance and compensatory hyperinsulinemia are primary events, and enhanced sympathetic activity and diminished adrenal medulary activity are important links between the defect in insulin action and the development of hypertension and the associated metabolic abnormalities.

Therefore, in view of the above and in view of the combined teaching of the prior art, an ordinary art skilled at the time the invention was made would have immediately envisaged the use of GH for treating insulin resistance in a patient having the Metabolic Syndrome exhibiting lipoprotein aberrations or hypertension in view of the teachings of the art, absent of objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDANCE

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272 0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

AAM Mohamed/AAM
September 27, 2004